RESPONSE

Applicant notes the absence of any cited references that anticipate the invention of the pending claims. Without acquiescence in the pending rejection under § 103, Applicant has amended the claims to define the nature of the invention related to the detection of the copy number of a plurality of genes in the genomic DNA of a patient's tissue sample, rather than the mere expression of a gene. The copy number of a gene is defined as the number of times a particular gene is represented in the entire genome. The copy number does not equate to levels of gene expression and a change in the copy number of a gene, that may accompany or cause disease, may not correlate with the change in expression (i.e. mRNA or protein level) of the gene. For example, a particular study observed that amplification of ERBB2 gene (6-8 copies) in prostate tumor does not result in the increased expression of the ERBB2 protein (Savinainen et al, Am J Pathol., 2002, 160:339-345).

Regarding the § 103 rejection over Chee (USP 5,840,484) and/or any of Seilhamer et al., Gao et al., Fukushima et al., Goetzl et al., Haapamaki et al., Gibbs et al., none of the claims are rendered obvious by any combination because a prima facie case under § 103 does not exist. Absent a prima facie case, one cannot draw the conclusion that the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. M.P.E.P. § 2142.

With respect to claim 17, the Chee et al. reference merely uses arrays of oligonucleotides as probes to detect mutations in a given sequence. Chee et al. do not make any assessment of a plurality of genes simultaneously and Chee et al. is specific to studying a single gene such as CFTR, p53 or RNA polymerase gene mutations. Moreover, Chee et al. rely solely on mRNA to study mutations and/or expression of a gene, Chee et al. do not disclose or suggest the detection in the

genomic DNA of a patient, of the copy numbers of a plurality of rationally selected genes, especially as here where the genes are part of a specific network of potential mutations having significance I a disease state.

Specifically, the present invention uses cDNA probes from a set of specific lipid associated genes that are related to, or are involved in, the manifestation of cancer and may be detected through the bioactive lipid framework. These genes are hybridized with genomic DNA in the patient sample to determine changes in the copy number of a particular gene. By definition, cancer is a genetic disorder (i.e. amplification and/or deletion of genes in genome) which is a consequence of genetic instability. While the expression levels (i.e. measuring the mRNA) of the genes can vary between cells, but the gene copy number may be stable for a given cancer at a given time.

None of the cited references suggest the approach of measuring copy number of the selected genes in a specific biological network. A rejection under §103(a) cannot be made absent a particular finding that justifies a conclusion that the skilled artisan would have had the motivation to combine or modify the cited references to reach the invention claimed. On this point, the MPEP states: "the mere fact that the references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." M.P.E.P. §2143.01. (See In Re Kotzab, infra.)

More particularly, Federal Circuit precedent requires that: "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *In re Kotzab*, 55 USPQ2d 1314, 1317 (Fed. Cir. 2000) (emphasis added). In the present case, no such finding can be made based on the implied or inherent teachings of Seilhamer et al., Chee et al., or any of the cited references, either alone or in combination, because none of the references contemplate the measurement of copy

number in a patient sample for the rational selection of genes in the bioactive lipid network. Seilhamer et al (USP 5,840,484) merely suggests the use of cDNA libraries followed by cDNA/mRNA hybridizations and does not teach any rationale for selecting genes associated with a particular biological pathway or mechanism and does not specify the use of patient genomic DNA with any particular set of genes. The rationale of Seilhamer et al. is to determine the relative abundance of gene transcripts (expressed mRNA) in two different biological samples and to identify one or more genes which are differentially expressed between the two samples. Because Seilhamer et al. do not specify particular genes, do not specify genomic DNA from a patient sample to hybridize to an array to determine alterations in copy number of a particular set (s) of the genes, and provides no express or implied suggestion for such an approach, this reference cannot possibly yield a § 103 rejection of the pending claims.

Gao et al. merely discuss the role of phospholipids within the arachidonic acid pathway. Again, this reference merely proposes to study the expression levels of some of the genes listed in the present claims. The published literature, especially by Goetzl et al., Haapamaki and Gibbs et al., teach the methods for detecting mRNAs for Edg receptors, PLA2 and PLD respectively, but do not mention any method or rational for determining copy number changes as in the present claims.

The failure of the cited references to suggest the selection of genes in a bioactive framework, or to use genomic DNA to measure copy, number actually demonstrates the inability to make the finding of facts on the record upon which a § 103 prima facie case could be based. The requirement for such evidence is unequivocal:

> We have noted that evidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved, see Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37

> USPQ2d 1626, 1630 (Fed. Cir. 1996), Para-Ordinance Mfg. v. SGS Imports Intern., Inc., 73 F.3d 1085, 1088, 37 USPQ2d 1237, 1240 (Fed. Cir. 1995), although "the suggestion more often comes from the teachings of the pertinent references,"Rouffet, 149 F.3d at 1355, 47 USPQ2d at 1456. The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. See, e.g., C.R. Bard, 157 F.3d at 1352, 48 USPQ2d at 1232. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence." . . .

In re Dembiezak, 50 USPQ2d 1614, 1617-1618 (Fed. Cir. 1999).

Finally, the claimed invention provides specific advantages over the art that are never contemplated by the references. Copy number changes in a particular set of genes will allow the tumor to be more precisely characterized or detected. Moreover the use of genomic hybridization (DNA:cDNA) may not necessitate the use of control samples because the DNA copy number is very stable and will alter only in disease conditions arising due to genomic instability such as cancer.

For all of these reasons, Applicant submits that the pending claims are not rendered obvious by any combination of the cited references, and are in condition for allowance.

Respectfully submitted,

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Dated: May 15, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

On page 5, starting with line 3, please replace with the following paragraph:

Gene amplification is a common mechanism leading to up-regulation of gene expression. (Stark et al., Cell. 75: 901-908 (1989).) Evidence from cytogenetic studies indicates that significant amplification occurs in over 50% of human breast cancers. (Saint-Ruf et al., supra.) A variety of oncogenes have been found to be amplified in human malignancies. Examples of the amplification of cellular oncogenes in human tumors are shown in Table 1 below.

TABLE 1

Amplified Gene	Tumor	Degree of Amplification
c-myc	Promyelocytic leukemia, cell line, HL60	20x
	Small-cell lung carcinoma cell lines	5-30x
N-myc	Primary neuroblastomas (stages III and IV) and neuroblastoma cell lines,	5-1000x
	Retinoblastoma cell line and pri[rn]mary tumors,	10-200x
	Small-cell lung carcinoma cell lines and tumors	50x
L-myc	Small-cell lung carcinoma cell lines and tumors	10-20x
c-myb	Acute myeloid leukemia	5-10x
	Colon carcinoma cell lines	10x
c-erbb	Epidermoid carcinoma cell	30x
	Primary gliomas	
c-K-ras-2	Primarycarcinomas of lung colon, bladder, and rectum	4-20x
N-ras	Mammary carcinoma cell line	5-10x

VERSION WITH MARKINGS TO SHOW CHANGES MADE

On page 6, lines 1-5, please replace with the following paragraph:

For example, as disclosed in U.S. Patent No. 5,846,749, the amplification of the Her-2 gene has been linked to invasive breast cancer phenotypes. In a study of node-negative invasive breast carcinomas, the degree of HER-2/neu gene amplification was determined by Southern blot analysis of EcoRI digested tumor tissue and the relative amount of HER-2/neu mRNA was determined by Northern hybridization of total RNA.

On page 8, line 22 to page 9, line 9, please replace with the following paragraph:

Restriction fragment length polymorphism (RFLP) studies have indicated that several tumor types have frequently lost heterozygosity at 13q, suggesting that one of the Rb-1 gene alleles has been lost due to a gross chromosomal deletion (Bowcock et al., Am. J. Hum. Genet., 46: 12 (1990)). The deletion of the short arm of chromosome 3 has been associated with several cancers, for example, small cell lung cancer, renal and ovarian cancers; it has been postulated that one or more putative tumor suppressor genes is or are located in the p region of chromosome 3 (ch. 3p) (Minna et al., Symposia on Q[O]uantitative Biology, Vol. LI: 843-853 (SCH Lab 1986); Cohen et al., N. Eng. J. Med., 301: 592-595 (1979); Bergerham et al., Cancer Res., 49: 13901396 (1989); Whang-Peng et al., Can. Genet. Cytogenet., II: 91-106 (1984; and Trent et al., Can. Genet. Cytogenet., 14: 153-161 (1985)).

VERSION WITH MARKINGS TO SHOW CHANGES MADE

On page 10, line 18, to page 11, line 4, please replace with the following paragraph:

Clinical classification utilizing the TNM system is based on evidence acquired before primary treatment. Pathologic classification includes the evidence acquired before treatment, as well as evidence acquired from surgery. The three components, T, M and N, are assessed. The use of numerical subsets of the TNM components indicates the progressive extent of the malignant disease. Any of the T, N, or M classifications can be divided into subgroups for testing. The TNM components can then be evaluated to determine the stage grouping (I-IV) of growth for the patient's cancer. The clinical stage is used as a guide to the selection of primary therapy, usually a form of surgery to remove the cancerous lesions. The pathologic stage can also be used as a guide for adjuvant therapy (chemotherapy), prognosis, and reporting end results.

On page 15, line 13 to page 16, line 17, please replace with the following paragraphs:

Other lysophospholipids associated with various conditions include lysophosphatidyl serine (LPS), lysophosphatidyl ethanolamine (LPE), lysophosphatidyl glycerol (LPG) and lysophosphatidyl inositol (LPI). Activated platelets secrete two kinds of phospholipase: sPLA2 and PS-PLA1. sPLA2 is reported to be elevated in inflammatory reactions and inhibition of this enzyme reduced inflammation. PS-PLA1 hydrolyzes phosphatidylserine or lysophosphatidyl serine (LPS) specifically to produce GPS or Glycerol-3-P serine. LPS strongly enhances degranulation of rat mast cells induced by concanavalin A and potentiates histamine release, and can stimulate sPLA2-elicited histamine release from rat serosal mast cells. LPS is an inflammatory lipid mediator and sPLA[Spla]2 has been implicated in inflammation processes. LPI has been shown to stimulate yeast

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adenylyl cyclase activity with implications for modulating the activity of downstream effector molecules and their interaction with RAS proteins.

Little is known about the mechanisms regulating LPA levels in vivo; however, the low LPA levels in[s] plasma indicate that production, metabolism or clearance is tightly controlled. LPA is a normal phospholipid constituent of all cells and functions as a metabolic intermediate in de novo synthesis of glycerophospholipids and triglycerides. As with other lipid mediators like diacylglycerol and phosphoinositides, the relationship between this "housekeeping" LPA and LPA that exerts its actions through cell surface receptors in unclear. Clearly a growing variety of cells including platelets, adipocytes, leukocytes, fibroblasts, endothelial cells and, ovarian cancer cells, can release LPA into the extracellular space in response to agonist stimulation. Phospholipase A2 (PLA2)-mediated deacylation of phosphatidic acid (PA), produced by the action of phospholipase D (PLD) on membrane phosphatidylcholine (PC) or by the actions of diacylglycerol kinase on diacylglycerol formed by phospholipase C likely contributes to LPA production in response to cellular activation. The pathway for production of extracellular LPA has been most intensely studied in platelets where release of membraneous microvesicles is a critical step.

On page 33, line 4, please replace with the following paragraph:

The term "immobilized on a solid support" means that the nucleic acid polymer is bound, covalently or through an affinity reaction, to a relatively contiguous surface. The solid support may consist of any appropriate material for binding nucleic acids, including glass, silicas, hydrogels (such as agarose or polyacrylamide), polymers (such as polystyrene or polypropylene), and cellulose derivatives (such as nitrocellulose). The solid support may be in any convenient form for quantifying

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the amount of hybridization, including beads, resins, microtiter wells, flat surfaces, rods, and the like. For use in the arrays of the present invention, flat silicate surfaces, such as used in U.S. Patent No. 5,744,305, are preferred. Immobilization formats adapted to these surfaces have been developed which can be easily loaded with the lipid associated gene probe sequences described in the invention, and which can be easily read with automated equipment.